Alzheimer's Association International Conference 2023 (AAIC 2023)

PGS session proposal

Title

Multi-polygenic score model informs the genetic basis of heterogeneity in Alzheimer's disease

Shortened Abstract Title

Multi-polygenic score for of heterogeneity in AD

Session proposal

- Session: “Multi-polygenic score model informs the genetic basis of heterogeneity in Alzheimer's disease”

Main

Background: Alzheimer’s Disease (AD) is a polygenic and multifaceted disease with many implicated biological pathways across diverse cell types. The heterogeneous phenotypic manifestation, beyond the common characteristic signature of Amyloid beta plaque, across cognition, pathology, and treatment response is well recognized. However, how the polygenic basis of the disease influences the disease heterogeneity across individuals at genomic and cellular levels remains largely uncharacterized.

Method: Here we develop multi- polygenic score (PGS) model to assess the genetic basis of molecular phenotypes associated with AD by systematically integrating large-scale single-cell RNA-seq profiling data of 1.9 million cells from 427 human subjects and hundreds of PGSs trained on more than 269,000 individuals in UK Biobank.

Result: We summarize commonly observed transcriptional changes associated with AD as 21 transcriptional hallmarks (Tx1-Tx21) by applying multivariate differential expression on single-cell profiling data. Each of our Tx hallmarks consists of dozens to hundreds of cell type-resolved gene expression patterns across six major cell types. Those 21 Tx hallmarks capture several known cellular and pathological signatures in AD, pinpointing their candidate driver genes, pathways, and cell types of action. Combinations of Tx hallmark burdens lead to a classification of our 427 donors into 14 AD and non-AD subtypes (G1-G14) with distinct phenotypic enrichments. For example, one of the AD groups (G5) driven by excitatory neuron-associated hallmarks shows elevated levels of amyloid burden (p-value = 6.4×10^{-3}) but minimum enrichment for tangles (p-value > 0.5) and cognitive measurements (p-value > 0.05).

We take advantage of pervasive pleiotropy and systematically assess the polygenic basis of Tx hallmarks by evaluating the cross-trait predictive performance of publicly available ancestry-matched PGS models across our 427 subjects. We find distinct patterns of PGS-Tx hallmark associations models, including cholesterol PGS models that predict oligodendrocyte Tx hallmarks, and volume of the gray matter in different regions of the brain predicts Tx hallmarks in excitatory and inhibitory neurons, indicating the ability to infer dysregulated AD hallmarks, risk groups, and subtypes across individuals decades before symptoms occur.

Conclusion: Overall, our results pave the way toward genetics-based prognosis and

transcriptional subtyping in complex and heterogeneous traits, even in inaccessible tissues.

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